Arthritis Advisory Committee

December 1, 1998

NDA 20-998 Celebrex™ (celecoxib) Searle

Volume I: FDA Medical Reviews

Medical Safety Review

DRAFT

NDA 20998 – Celecoxib Safety Review

Reviewer: Maria Lourdes Villalba, MD
11/4/98

This NDA Integrated Safety Summary contains safety data from 51 studies, with a total enrollment of 18,439 subjects (13,072 individuals) of whom close to 9400 have received at least one dose of Celecoxib (Cx). With the exception of one continuing long-term open label study, the clinical studies included for analysis were completed by the end of April 1998. Two completed Japanese trials, ongoing trials and trials under other INDs are not included in the ISS analysis.

For the purpose of data presentation and analysis, the studies are grouped into the categories shown in Text Table 1 of the ISS: "**Phase I**" (single dose, multiple dose, drug interaction, hepatic impairment, and renal impairment), "**Arthritis**" (subcategorized as OA, RA, combined OA and RA, and long-term open label), and "**Analgesia**" (subcategorized as dental pain and surgical pain). I reviewed Phase I studies and the arthritis trials.

Text Table 1. Studies in Celecoxib Clinical Program Included in this Summary

Type of Study	No. of Studies	Study Numbers
Phase I		
Single dose	9	001, 006, 009, 018, 019, 037, 044, 084, 088
Multiple dose	11	003, 004, 010, 014, 015, 026, 032, 033, 043, 065, 069
Drug interaction	7	017, 038, 039, 040, 050, 051, 072
Hepatic impairment	1	016
Renal impairment	1	036
Arthritis		
OA		
Pivotal efficacy	5	020, 021, 054, 060, 087
Supportive	3	042, 013, 047
RA		
Pivotal efficacy	2	022, 023
Supportive	2	041, 012
OA/RA combined	2	062, 071
Long-term open label	1	024
Postsurgical analgesia		
Dental pain		
Pivotal efficacy	3	025, 027, 070
Supportive	1	005
Surgical pain		
Pivotal efficacy	1	028
Supportive	2	029, 080
Total	**51**	

Derived from Tables 1.1 through 1.5.

Dose and duration of exposure to Cx: Single dose studies were performed with doses ranging from 5mg p.o. to 1200 mg p.o. The highest doses used for multiple dose pharmacologic studies were up to 600 mg twice a day for 8 days. Chronic dosing in arthritis patients ranged from 100 mg BID to 400 mg bid for 24 months (2 ex-US combined OA/RA trials). Adverse experiences were monitored during study visits and by diary cards reviewed at each study visit. Adverse events included signs or symptoms, clinically significant laboratory abnormalities, or any abnormality detected during physical examination. All data on each adverse event were recorded onto a case report form along with the Investigator's opinion of intensity: mild, moderate and severe; seriousness (FDA definition) and relationship to study drug (none, uncertain, probable). Relationship to study drug was also evaluated by a Searle Medical Monitor. Terms used by the investigators to describe each adverse event were translated into the World Health Organization Adverse Reaction (WHOa.r.t.) terminology. In the arthritis studies, symptoms of arthritis of the type under study in a given trial were generally not considered as adverse events, except if they met the criteria for a serious event. Similarly, in the surgical analgesia studies, pain arising from the surgical procedure was not considered to be an adverse event. In the studies in which routine UGI endoscopies were performed, only symptomatic patients were considered to have had an adverse event, but all of the data related to the ulcer were included in the analyses of endoscopy findings.

Phase I trials –

Single dose studies:

Nine single dose studies involved a total of 312 healthy subjects (248 men, 64 women), ages 18 to 55, who received single oral doses of Cx of 5, 25, 50, 100, 200, 300, 400, 600, 800, 900 or 1200 mg. All studies were randomized. Seven studies were open label crossover studies, comparing different Cx doses or different Cx formulations; studies 001 and 009 were double-blind, placebo controlled; study 009 included ibuprofen as an active comparator. There were very few adverse events; there were no serious adverse events; two events causing withdrawal (mild toothache and appendictis following a single dose of Cx 200 mg, in study 084) were not considered to be related to study medication.

Two subjects in the 900 mg group (study 001), experienced elevation of liver enzymes. Laboratory values returned within the normal range within three to eight days of dosing for both of these subjects; additionally, laboratory values following re-challenge of the 900 mg dose in one of the subjects were all within the normal ranges.

Multiple Dose studies

Phase I Multiple Dose studies included a total of eleven studies. All studies were randomized; seven were DB, three open label and one single blind; seven studies were placebo-controlled and five were active comparator-controlled. In addition to clinical evaluation, laboratory and adverse events monitoring, Study 014 included endoscopic examinations. Most adverse events were mild or moderate in severity. There were no serious adverse events during these trials.

There were only four withdrawals due to adverse events. Two subjects (one in the Cx 40 mg and one in the Cx 200 mg), were withdrawn from study 003 due to abnormal labs (increased creatine kinase and increased SGOT, respectively). A young placebo subject with prepatellar bursitis was withdrew from study 015, ("Comparison of the SC-58635 PK profile in Elderly and Young subjects"). One patient with headaches withdrew from the ibuprofen arm in study 065.

Drug interaction studies - There were seven pharmacokinetic interaction studies: 017(with MTX in women with RA); 038 (with lithium carbonate in healthy adults); 039 (with glyburide in subjects with Type II Diabetes Mellitus), 040 (with warfarin), 050 (with diphenylhydantoin in healthy subjects), 051 (with tolbutamide in healthy subjects), 072 (with fluconazole and ketoconazole in healthy subjects).

[Of note, there were no formal interaction studies with ASPIRIN].

Two subjects in study 050 and five subjects in study 072 (3 in the fluconazole group and two in the ketoconazole group) had clinically relevant changes in hematocrit levels (≥ 5%) at post-treatment. These changes were attributed to study-related phlebotomy.

Most adverse events were mild or moderate in severity. There was only one serious adverse event and it was not related to study drug (appendicitis in study 071). One subject withdrew from study 038 because of a urinary tract infection that required medication not permitted in the study. One placebo subject withdrew from the study 039 due to hypoglycemia. There were no deaths.

Clinical and laboratory data in patients with very high concentration of Celecoxib. The FDA PK team was concerned about possible adverse events among 6 patients who presented particularly high plasma concentrations of Celecoxib. Our review revealed no outstanding adverse events (Table), however safety laboratory studies were obtained after 48 hours and some transient effect could have been missed. Lab measurements were done at : Study 015: baseline, day 2, 4, 6, 8, 10, 12 and 14 post dose

065: baseline, day 4 and day 8 post dose

072: baseline and 3 weeks post dose

020: baseline, 2, 6 and 12 weeks post dose.

Table 2. Clinical manifestations and laboratory of patients with high celecoxib plasma concentrations.

Patient/ trial	Gender/ race/age	Celecoxib dose (mg)	Signs/ Symptoms	Hematology	Electrolytes	LFT's
221/015	73 C F	200 BID	Urticaria (d2) Diarrhea (d4) Sinusitis (d6)	(b)(4)		
222/015	68 C F	200 BID	Intermittent dizziness			
012/065	33 C M	600 BID				
031/072	33 C M	200 SD	Eye pain, peri orbital discomfort			
827/020	68 B F	100 BID				
461/020	80 B F	200 BID				

Hepatic Impairment. Study 016 was an open label, randomized, single and multiple dose PK evaluation study of Celecoxib in subjects with and without hepatic impairment in 12 mildly hepatically impaired subjects; 11 moderately hepatically impaired; and 25 normal subjects. Subjects were given one Cx 100 mg capsule on day 1 and 8, and one 100 mg capsule BID on days 4 to7. Most adverse events were mild and with the exception of two cases of diarrhea and one case of dyspepsia, were determined to be unrelated to the study drug. There were no withdrawals and no deaths. No significant laboratory changes.

Renal Impairment. Study 036 was a randomized, DB, PC and AC, parallel study of **75 subjects** (36 men, 39 women) ages 39 to 81, with stable chronic renal insufficiency, who received **SC 200 mg BID,** naproxen 500 mg BID for **seven days,** or placebo on days 1 to 6 and a single morning dose on day 7. There were no serious adverse events and no deaths. Two withdrawals in the placebo group (one headache, one confusion) were not considered to be related to study drug.

[In summary, from the phase 1 studies, Celecoxib appears to have an acceptable safety profile at doses explored . Most adverse events were mild or moderate, there were a few withdrawals and serious adverse events, most of them probably unrelated to the drug, and there were no deaths. Two patients presented reversible elevation of LFT's after a single dose of Cx, 900 mg.

Six patients who showed very high Cx plasma concentrations, had not particularly worrisome clinical or laboratory adverse event.

Regarding the 7 patients who showed clinically significant drop in hematocrit in study 050 and 072, it is not completely clear to me whether it was just due to repeated flebotomy or if there is another explanation. In this study fluconazole and ketoconazole significantly affected Cx metabolism.

In study 016, 23 patients with hepatic impairment received Cx 100 mg BID for 4 days. Hepatic impairment resulted in an increased mean trough concentration with greater hepatic impairment associated with increased mean trough plasma concentrations. Celecoxib was well tolerated without significant changes in LFT's. Does it mean that patients will similarly tolerate 200 mg BID for longer periods? Does this justify the "no need for dose adjustment" in patients with mild to moderate hepatic impairment? Additionally, patients with severe impairment were not studied.

In study 036, 40 patients with stable chronic renal insufficiency tolerated Cx 200 mg BID for 7 days. Again, this is a short period and Cx should be used with caution in patients with renal disease].

Arthritis trials – O.A, R.A and combined trials.

Osteoarthritis trials (eight trials: 020, 021, 054, 013, 042, 047, 060, 087)

Two to six-week OA studies.

There were five randomized, double blind, multi-center, parallel studies, that compared different doses of Celecoxib (ranging from 25 mg BID to 400 mg BID for 4 weeks and 200 QD for 6 weeks) to placebo, in patients with OA of the knee in a flare state (013, 047, 060, 087), or to an active comparator (diclofenac 50 mg BID) in patients with OA of the hip or knee of more than 6 months (study 042). 2787 patients were randomized (843 men, 1944 women); 2479 Caucasian, 218 Black, 61 Hispanic, 11 Asian, 18 Other. 2778 patients actually received at least one dose of study drug.

Table 3. Randomization in two to six-week OA studies

Treatment	Study 013 (2 weeks)	Study 042 (6 weeks)	Study 047 (4 weeks)	Study 060 (6 weeks)	Study 087 (6 weeks)
Placebo	71		101	232	244
Cx 25 or 40 mg bid	73		101		
Cx 100 mg bid or 200 mg q.d.	76	347	101	454	474
Cx 200 mg bid	76				
Cx 400 mg bid			99		
Diclofen 50 mg bid		341			
total	293	688	402	686	718

APPEARS THIS WAY ON ORIGINAL

Table 4. Two to six week OA trials. Adverse events requiring withdrawal and serious adverse events, (013 (2w), 047(4w), 042, 060, 087(6w)). S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients	Placebo N= **648**	SC 25 or 40 mg BID N=**174**	SC 100 mg BID or 200 QD N=**1452**	SC 200 mg BID N=**76**	SC 400 mg BID N=**99**	Diclofenac 50 mg BID N=**341**
Dyspepsia	1		2		1	1
Diarrhea	2		3		1	5
Abdominal Pain	6	1	5			7
Nausea/vomiting	4		9			2
Esophagitis/gastritis						1
G.I. bleeding		1 N S (rec)				
Abdominal fullnes, nausea			1			
Palpitations			2 (one arr S N,)	1 (arr) SN		
CHF			1 S N			
Chest pain, CAD	1 (MI) S N	1 N,	1 S, 1 S N, DEATH			
Headache	1		1 N			1
Dizziness	2		3 N,			
Hyperesthesia, numbness, tingling	1		2 N			
Anxiety/irritabilit	1		1			
Insomnia			1			
Rash/urticaria/ allergic reaction	4 (one S)	1	11	1	2	1
Skin lesion			1			
Pruritus	1			1	2	
Back pain			2 N			
Arthralgia/myalgia	1 1 N				1	
Peripheral pain	1 N	1 N	2 N.			1 N
Accidental injury	2 N,		1 N S			1
Malignancy	2 S N,					
Hematuria						1 N
Fatigue	1					1
Dyspnea			1 N			
Respiratory inf: URI, bronchitis pneumonia,	1 N		2 N			1
Broncospasm		1	1 S			
Phlebitis						1 N
Weight gain			1			
Alopecia			1 N			
Hemol uremic S.					1 S N	
Edema	1 (face)		2			1
Renal insuff	1 N					
Septic arthritis			1 S N			
Herpes Zoster			1 S N			
Stomatitis			1 N			
Dry mouth	1 N					
Tox due to Non study drug	1 S					

Hyperglycemia			1 S			
Elevated CPK	2 N		1 N			
Elevated SGOT/SGPT						3
Decreased WBC						1
Hyperkalemia					1	
Anemia			1			

Serious events with no withdrawal:

Trial 013: none
Trial 042: Diclofenac: 1 angina N, 1 shceduled TKR N
Trial 047: Placebo 1 Lung Ca N.
Celecoxib 25 bid – 1 rectal hemorrhage N.
Cx 100 bid – 1 chest pain and bronchospasm N
Trial 060: Placebo Urinary incontinence N
Cx 100 bid – 1 CHF N, 1 CVA N
Trial 087: Cx 200 QD – 1 basal cell Ca. N.

APPEARS THIS WAY ON ORIGINAL

12 week OA trials

Included three double-blind, placebo-controlled and active-controlled, multicenter (U.S. and Canada), parallel studies with a total of 3268 patients, ages 19 to 93, with OA of the knee (020 and 021) or hip (054) in a flare state, randomized to receive SC-58635 50 mg capsules BID (671), 100 mg BID (644) or 200 mg BID(1114); Naproxen 500 mg BID; or placebo, for 12 weeks. Adverse events requiring withdrawal are shown in Tables 020, 021 and 054. There was only one serious event considered to be related to the study drug (patient in study 054 with abdominal pain and possible ileus). There were no deaths.

Table 5. Randomization in 12-week OA studies:

	Study 020	Study 021	Study 054	Total
Placebo (n)	204	242	218	664
Celecoxib 50 bid	203	252	216	671
Celecoxib 100 bid	197	240	207	644
Celecoxib 200 bid	202	233	213	648
Naproxen	198	226	207	631

APPEARS THIS WAY ON ORIGINAL

Table 6. Adverse events requiring withdrawal, study 020, 021, 054 .

S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients	Placebo N=**664**	SC 50 mg BID N=**667**	SC 100 mg BID N=**644**	SC 200 mg BID N=**648**	Naproxen 500 mg BID N=**631**
Dyspepsia	6	6	10	9	16
Diarrhea	2	5	4	3	3
Abdominal Pain	2	8	5 (+ one pt with abd abcess, N)	9	18
Nausea/vomiting	6	3	4	2	8
Obstruction	1 (intest gangrena) SN	1 small bowel S N	1 small bowel S N		
Upper G.I. bleeding	1		1 (gastric ulcer)		5 one S
Abdominal fullnes, flatulence			1	1	2
Pancreatitis			1 S N		
Stomatitis		0136 N			
Rectal burning			1		
Palpitations/arrhyt	1 A.fib N,	2 (one SVT SN)	2		1
CAD	1		1 S N	3 S N	1 S N
CHF				1 S N	
HTN/aggr HTN			1	4 (one S, two N)	
Headache	2	3	3 (2 N)	1	1
Dizziness	1	1	3	2	1
Tinnitus			1	2 N	
Depression/ somnolence			2 N	1	2
Anxiety/irritability/ insomnia		1	3	2	
Abnormal gait				1 N	
Hypersthesia/numb			1		
CVA	1	1 N	2 N	1 (w/ HTN)	
Rash/urticaria/aller gic reaction	1	9	7 (one had swollen lips)	14	8
Pruritus	1		2	1	
Bronchospasm	1	1 N			
Skin lesion			0284 N dermatitis)		
Herpes Zoster			0857 N		
Arthralgia/myalgia	2	1	2 N	1 N	
Back pain	4	1	3 N	2 N	1
Peripheral pain			1 N	1 N	
Accidental injury	2	1 N	2 S N		3 N
Miscellaneous rheum. complaints	1	1 SN	2 N (one gout attack)	1	
Malignancy	2	1 S N	3 S N	1 S N	2 S N
Fatigue	1		1	2 N	
Dyspnea	1				
Pulm embolism				1 S N	2 S N
URI/Bronchitis/ pneumonia	1 N	1 N		2 N (one S pneumonia)	
Edema	1		2 N (one face ede)		
Flebitis		1 N			
Miscell.		1 goiter N		1 temp arteritis	1 fibroids, 1 ecchym, 1 hyperglyc
Elevated CPK			1 N		
Elev. Creatinine		1+ proteinuria and peripheral edema		1	
↑ SGOT/SGPT	1		1		

Anemia		1	1 + proteinuria and thrombocytemia		3
Leukopenia	1 N				

RA trials **Rheumatoid Arthritis Trials** (022, 023, 041, 012).

The RA trials were multicenter, randomized, double blind, parallel studies involving a total of 3237 patients (863 men, 2374 women), ages 20 to 90, (2828 Caucasian, 208 Black, 161 Hispanic, 19 Asian , 21 other) with RA in a flare state (012, 022 and 023) or with stable RA (041), who received Celecoxib ranging from 40 mg BID for four weeks up to 400 mg BID for 12 weeks and 200 mg BID for 24 weeks.

Table 7. Randomization in RA trials

Treatment	Study 012 (4 weeks)	Study 022 and 023* (12 weeks)	Study 041** (24 weeks)
Placebo	85	452	
Cx 40 mg bid	81		
Cx 100 mg bid		468	
Cx 200 mg bid	82	453	326
Cx 400 mg bid	82	434	
Naprox 500 mg bid		443	
Diclofenac SR 75 mg bid			329
total	330	2250	655

*Studies 022 and 023 had similar design. Study 022 specifically evaluated UGI safety and involved patients with no significant lesions on endoscopy. ** Study 041 was an ex-US study (Australia, Europe, South Africa, New Zealand and Israel) evaluate that also particularly evaluated GI safety.

Table 8. RA trials. Adverse events requiring withdrawal and serious adverse events, (012 (4 w), 022, 023 (12 w), 41(24 w)) S = Serious event. N = found to be not related to study drug by Searle Medical Monitor.

Total number of patients	Placebo **N=537**	40 mg BID N=**81**	SC 100 mg BID **N=468**	SC 200 mg BID N=**862**	SC 400 mg BID **N=951**	Naproxen 500 BID N= **443** , or Diclofenac 75 mg BID (*D*) N=**329**
Dyspepsia	2	1	3	5	5	6 (one S)+ *8 D*
Diarrhea	1		1	6	2	*5 + 5 D*
Abdominal Pain	2		4	10	1	*7 + 27 D*
Nausea/vomiting	1			5	1	*1 + 3 D*
Esophagitis/gastritis				1		
Rectal burning						
S.Bowel obstruct						*1 D* N
G.I. bleeding/ ulcer				1		*6 D (one S)*
Abdominal fullnes, flatulence					1	*2 D*
Palpitations				1 N	2	
SVT						
CHF				1 N		
Chest pain, CAD	1 SN, 1(MI),SN		2 S (one MI, N)	1 S N		1 N
Headache	3			2	1	*1 D*
Dizziness				1+ headac & face edema	1	*2 + 2 D*
Tinnitus	1		1 (+ otitis med & periorb edema)		2	1
Hyperesthesia, numbness, tingling				0428/22 N		
Depression/somnolence	1			0333/23,		1 + *1 D* S
Anxiety/irritabilit			1			*1 D*
CVA				0598/41 SN		1 SN
Rash/urticaria/allergic reaction	6 + 1 (+ face edema & broncosp)		4	**16** (one w/ periorb edema, one w/ face edema, one w/ **angioedema)**	**12** (one w/ swollen face and **laringeal edema**, one w/ face edema, one w/ sob, two w/ numbness & paresthesias, one w/ rigors & chills, one w/ **anaphylactoid react** N),	3 + *1 D*
Pruritus			3			
Bronchospasm	1					
Skin disorder				**2 skin ulceration** N. **1 fingertip excoriations** N.	**1 skin ulcer** (diabetic ulcer). **1 vasculitic lesions** both hands 1 contact dermatitis	
Accidental injury					1 SN	
Malignancy			1 SN	2 S N (one DEATH)	1 SN	
Fatigue			1	2		
Dyspnea				1		
Pulm embolism						*1 D* SN
Respiratory inf: URI, bronchitis pneumonia,	1			3 N		

Phlebitis						*2 D* N
Edema	face 1			1 Face & mouth	1 periph	1
Leg cramps			1	1		
Hematuria						
Kidney stone	1 SN					
Stomatitis				1		
Miscell.					1 epistaxis	*1 D* S N (recto vesical fistula)

Elev. BUN/creatinine				0519/41		*2 D*
Elevated SGOT/SGPT			0288/22	0915/23		
Hipokalemia			0663/23			
Anemia				0785/22 N (+ thrombocytemia		*1 D* S

Serious Adverse Events without withdrawal:

Trial 012: none

Trial 023:
0501 Myocardial Infarction , SC 200 bid (N)
0757 Basal skin cell ca. Naproxen
0485 Accidental injury, diabetic, gangrenous toe (SC 200 bid) (N)
One patient with colon CA in SC 100 bid
1137 Cholecystitis on placebo

Additional adverse event of note in trial 023: # 0895 (neuropathy, syncope (N), fungal infection ringworm)

Trial 022:
Placebo: 0558 chest pain , 2 skin malignancy N
Naproxen 500 mg bid: 0042 facial cellulitis , aggravated RA 1 patient
Celecoxib: 0921 upper resp. infection. N. SC 100 bid,
0462 pneumonia N SC 200 bid, 1625 bronchitis N SC 200 bid
0921 upper resp. infection. N. SC 100 bid,
0212 angina pectoris – SC 400 bid,
0683 aggravated HTN (N) SC 400 bid

Trial 041:
Diclofenac 75 mg bid: 1 back pain, 1 lymphangitis, 1 gastroenteritis,1 CTS release, 1 amputation of little toe, 1 cellulitis. 1 pyometra.
Celecoxib 200mg bid: 0790 Septic arthritis (post op) "shoulder sepsis" S N.
0126 Myocardial Infarction. S N. 0039 depression S N.
0707 dyspnea. 0202 and 0093 pneumonia S N.
0481 , 0892 and 0157 accidental injury S N.
0011 anemia + pleural eff

COMBINED OA AND RA.

Table 9. Adverse events requiring withdrawal and serious adverse events (062 and 071 (24 weeks, ex US)) S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients		Cx 200 mg BID N = **636**	Ibuprofen 800 mg TID N = **346**	Diclofenac 75 mg BID N = **387**	Naproxen 500 bid N = **267**
Dyspepsia		2	3	11	2
Diarrhea		1		4	
Abdominal Pain		3	7	8 (one N)	6
Nausea/vomiting		4	5	2	2
Constipation				1	
Esophagitis/gastritis/ gerd		2		2	3
S.Bowel obstruct					1 S
G.I. bleeding/ gastric ,duodenal, esoph ulceration		2 S (one intestinal perforation N).	7	7 (two N)	5
Abdominal fullnes, flatulence			1	1	
Palpitations		1/71		1	1S (arr), 1 S N
SVT					
CHF		1/71			
Chest pain, CAD		**3/62 S N**	1/71 MI S N	1/62 S N	1 MI, S N
Syncope/ sudden death		1/71	1/71 sudden **DEATH, S N**		
Hypertension		1 S		1 N, 1 **DEATH , S N**	1 N
Hypotension			1 hypoten		
Dizziness			3/71		1
Tinnitus/deafness		1			
Hyperesthesia, numbness, tingling				2 (one N)	
Depression/somnolence			1/71	1	
Abnormal gait/ dystonia		1			
CVA					1 **DEATH** (brain stem infarct) S N
Rash/urticaria/allergic reaction Skin disorder		2 (one N)	2/71	2 (one **anaph shock)** 1 soft tissue infection N	3
Arthralgia/myalgia/ worsening arthritis					1
Accidental injury		2		1 S N	
Malignancy		1 S N.		1 S N	
Dyspnea		**1**	1	1 COPD exac S N	1 N
Respiratory inf: URI, bronchitis pneumonia,		2 (one otitis media + deafness) N		1 S N	
Cough			1		
Pleural eff					**1/71 S N (empyema D)**
Edema			Face 1/71	Face 2/71	Face 1/62,
Miscell		1 S N (kidney stone)		1 Breast enlargement	

Urinary infection		1 N			1 SN

Elev. BUN/creatinine			1		1
Abnormal liver, ↑SGOT/SGPT		1			3
Anemia			3		1

Serious AE without withdrawal:

Trial 062:
Naproxen: 2 dyspnea, 1 SVT, 1 intestinal obstruction
Celecoxib 200 bid: 1 psychotic episode N, 1 aggravated hypertensionN, 1 pleural effusion N

Trial 071

Ibuprofen 800 mg TID: 1 pyelonephritis, 1 emergent surgery
Diclofenac 75 mg BID: 1 Angina pectoris, 1 Copd exacerbation, 1 atrial flutter, 1 scheduled surgery
Celecoxib 200 mg bid: 1 urinary infection N, 1 basal cell ca N, 1 depression aggravated, 1 scheduled surgery, 1 emergent surgery.

Data analysis

After an initial safety review of all the controlled arthritis trials, statistical comparison of the number of selected serious adverse events and adverse events causing withdrawal for Celecoxib (50 to 400 mg BID doses), placebo and active comparators, was requested to Searle on 10/28/98 and provided to FDA on 11/2/98.

All OA, RA and combined OA/RA trials were divided in two groups:
a) < 12 weeks duration (012, 013, 042, 047, 060, 087)
b) ≥ 12 weeks duration (020, 021, 022, 023, 041, 054, 062, 071)

We requested the following categories:

I - Gastrointestinal
a) Hard GI endpoints (perforation, obstruction, UGI bleeding)
b) Dyspepsia
c) Abdominal pain
d) Nausea

II - Cardiovascular:
a) Palpitations, arrhythmia
b) Congestive heart failure
c) Angina/ coronary artery disease/ cardiac chest pain
d) Hypertension/ aggravated hypertension

III – Skin
a) rash, urticaria, allergic skin reaction, dermatitis
b) skin ulceration/skin lesion (exclude skin malignancies)

IV – Allergic reaction (excluding skin rash)/ anaphylactoid reaction/ anaphylactic shock, bronchospasm/ asthma/ angioedema

V – Infections
a) respiratory (otitis, rhinitis, pharyngitis, upper respiratory, sinusitis, bronchitis, pneumonia)
b) urinary (cystitis, bladder, kidney, pyelonephritis)
c) sepsis
d) septic arthritis, joint infection
e) skin infection, herpes zoster

Summary of the analysis performed by Searle, based on Searle's database (need to fill out the numbers) (my numbers may look different because some patients withdrew with more than one event and I chose only one, may be different from the one chosen by Searle):

Gastrointestinal adverse events: For >= 12 week trials.

For major GI events: (Perforation, Ulcers and Upper GI Bleeding) serious and causing withdrawal, there was a statistically significant difference in favor of Celecoxib when compared to active comparators. There was no difference between active comparators and placebo.

For dyspepsia and abdominal pain requiring withdrawal, there was a significant difference between active comparators and Cx and active comparators and placebo.

For <12 week trials: The incidence of dyspepsia, nausea and abdominal pain severe enough to require withdrawal was neither different to placebo nor to the active comparators.

[Celecoxib a the doses proposed (100 and 200 mg BID) seems to have a safety profile superior to other NSAIDs regarding the incidence of major GI complications. Of note, there were "minor" GI side effects, still bad enough to require withdrawal in 1 to 3% of patients] [Again, these data comes from Searle's database; Dr. Goldkin , the Gi reviewer has different data].

Of note, there was no significant number of patients withdrawn due to elevated liver function test and this analysis was not requested to the company. However, it may be worth it to look at LFT's in patients withdrawn due to other GI adverse events]

Cardiovascular events:
Among the ≥ 12 week trials there were 16 CAD related events among patients on Celecoxib (0.4%), 5 among active controls (0.2%) and 6 among placebo (0.5 %). The differences were not statistically significant. The incidence of arrhythmia was < 0.1 % for all groups.

<12 week trials, the incidence of CAD related events and for arrhythmia was 0.1 % or less for all groups.

Skin ulceration– In the November 2 Searle's database there was only one case of skin ulcer in a placebo <12 w patient. Among the skin lesions causing withdrawal there was 1 in Cx 200mg bid in the ≥ 12 w trial's (one case of a patient with a diabetic ulcer and a gangrenous toe).

[Additionally I found 3 cases of Skin Ulceration, 1 case of skin vasculitis, 1 case of "excoriation of the fingertips", 1 case of "contact dermatitis". The nature of these skin lesions is not clear to me. Were they allergic, infectious, ischemic? There were also at least 2 cases of nasal septum ulceration among RA patients reported as non serious and no requiring withdrawal.
Of note, unexplained skin lesions have been observed in dogs at higher doses, not used in humans with celecoxib and with other COX 2 inhibitors].

Allergy - There was a high incidence of different kind of skin rashes. I think that these rashes were mostly allergic and should alert us to the possibility of more severe allergic reactions.

[The pathophysiologic mechanism responsible for NSAID-induced allergy is not known. It is thought to depend on inhibition of cycloxigenase (COX 1, 2 or both?) coupled with upregulation of 5-lipoxigenase dependent pathways.

Two cases of bronchospasm were seen among placebo. No major allergic reactions were seen in the active comparator group. However there were cases of angioedema, laryngeal edema, bronchospasm, and anaphylactoid reaction (1 each) among Celecoxib patients. These trials were not powered to detect infrequent adverse events particularly among the active comparators. Additionally these trials excluded patients with known allergy to NSAID and sulfa drugs.

Celecoxib should be used with caution in people with known allergy to other NSAIDs and sulfa drugs].

Incidence of serious infections – There were no statistically significant differences in the number of serious events or infections requiring withdrawal among the Cx compared to placebo and active comparators.

Renal – Regarding renal adverse events and laboratory, Celecoxib has a safety profile comparable to a mild NSAID. The significance of the mild increase in chloride among Celecoxib patients, particularly without bicarbonate data is difficult to

interpret. The three special renal studies were underpowered to detect infrequent serious adverse events; even active comparators appeared to be benign to the kidney.

[redacted]
APPEARS THIS WAY ON ORIGINAL